

Depleted Uranium (DU) Follow-Up Program Update



Melissa A. McDiarmid, MD, MPH, DABT
Katherine S. Squibb, PhD
VA Maryland Health Care System
University of Maryland
Baltimore, USA

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Gulf War Exposures to DU

- **Friendly-fire incidents exposed US soldiers to:**
 - **DU shrapnel**
 - **Aerosolized DU oxides**
 - **Inhalation, ingestion, wound contamination**



- **Burning of munitions storage facility**
- **Decontamination of military equipment**

Purpose of DU Surveillance Program

- Determine DU-related health effects, if any, in exposed soldiers
- Develop methods to measure uranium exposure
 - Inhalation exposure/wound contamination
 - Embedded fragment
- Examine medical and surgical management of fragments



Measurements of DU Exposure

- Urine uranium concentrations
 - Relation between fragment status and elevated urinary uranium levels first observed in 1994 visit
 - Confirmed in all 7 subsequent visits
- Developed analytical method for measuring DU vs total U
 - U^{235}/U^{238} isotopic analysis

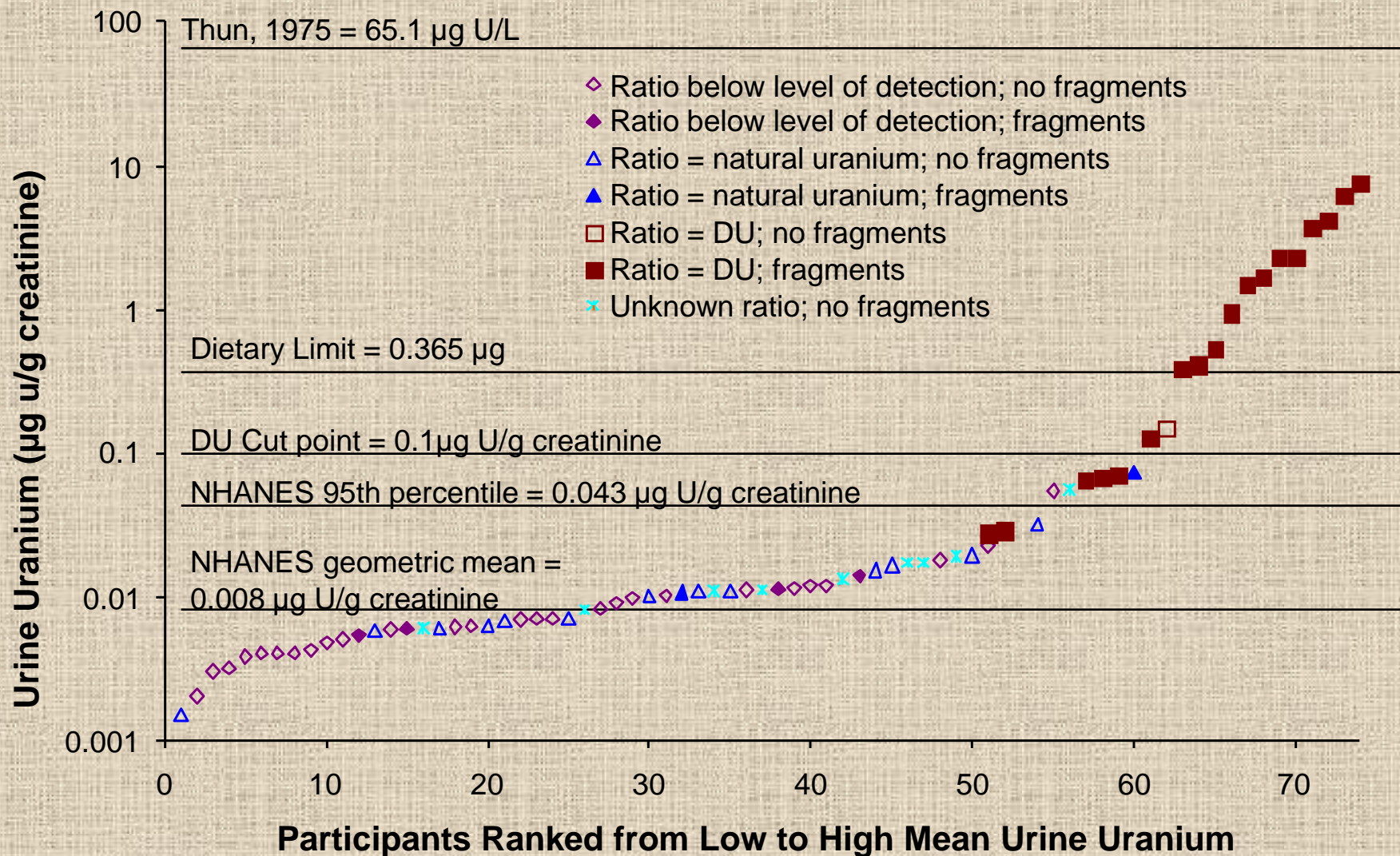
Summary of Surveillance Visits

<u>Visit Year</u>	<u>Gulf War I</u>		<u>OIF</u>	<u>Total</u>
	<u>DU-exposed</u>	<u>Non-exposed</u>	<u>DU-exposed</u>	
1993-4	33			33
1997	29	38		57
1999	21 + 29 new			50
2001	31 + 8 new			39
2003	32			32
2005	30 + 4 new		3	37
2007	32 + 3 new		2 (1 new)	37
2009	38 + 2 new		2	40

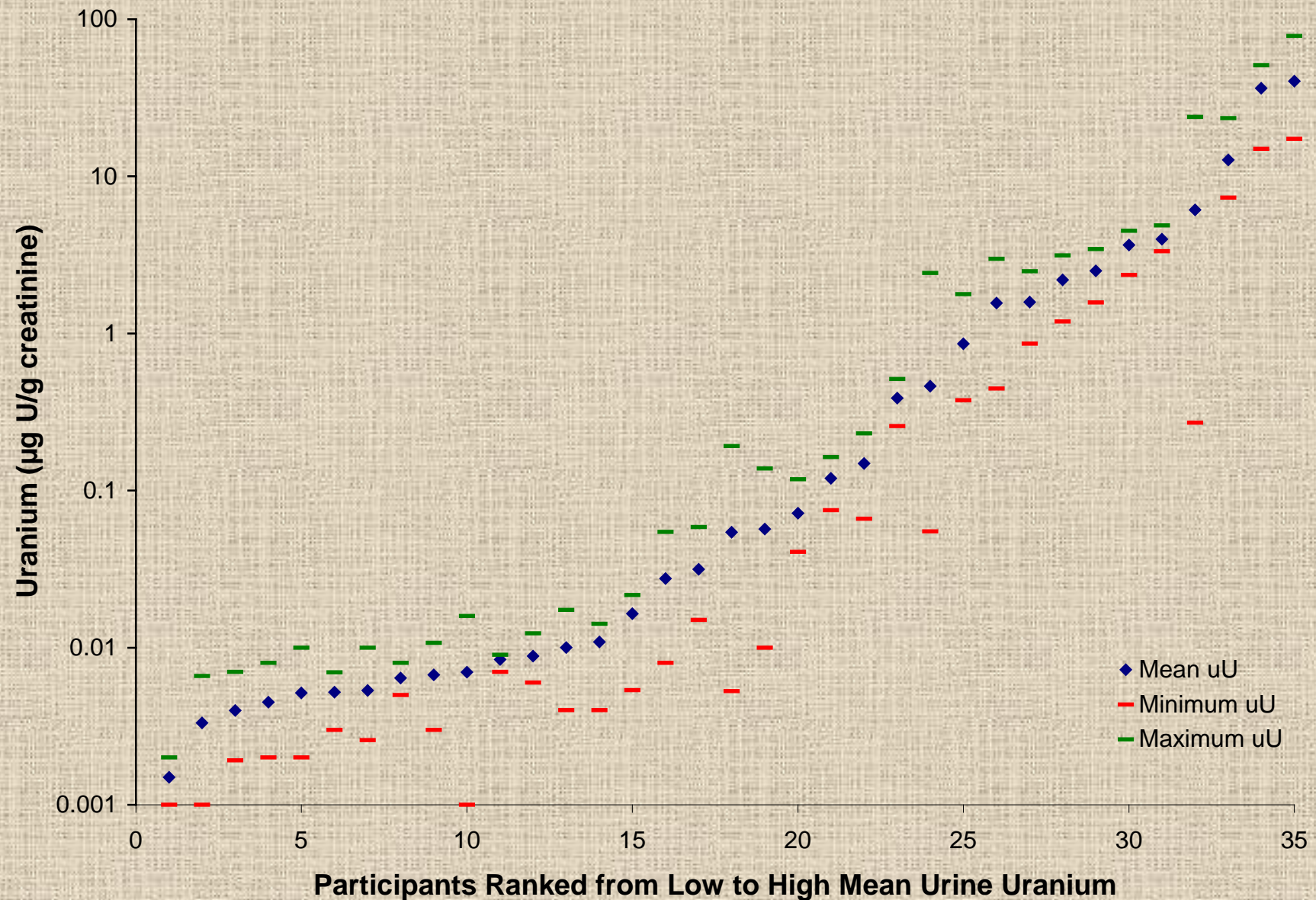
79 unique cases have been evaluated from Gulf War I.

4 unique cases have been evaluated from OIF.

Mean Urine Uranium Values (1993-2007, N=77)

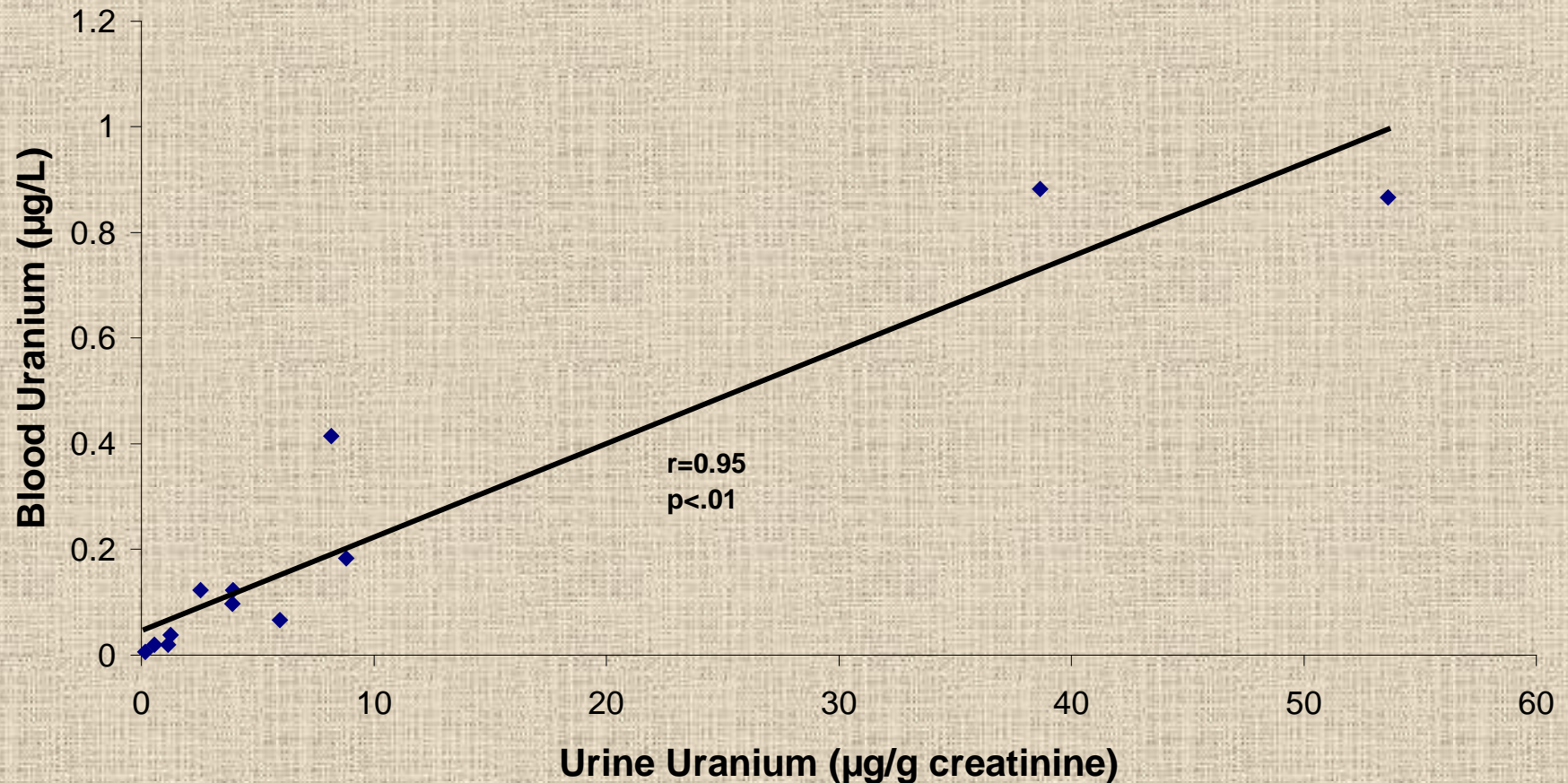


Individual Participant's with 4 or More Visits Mean uU with Minimum and Maximum uU Values (n=35)

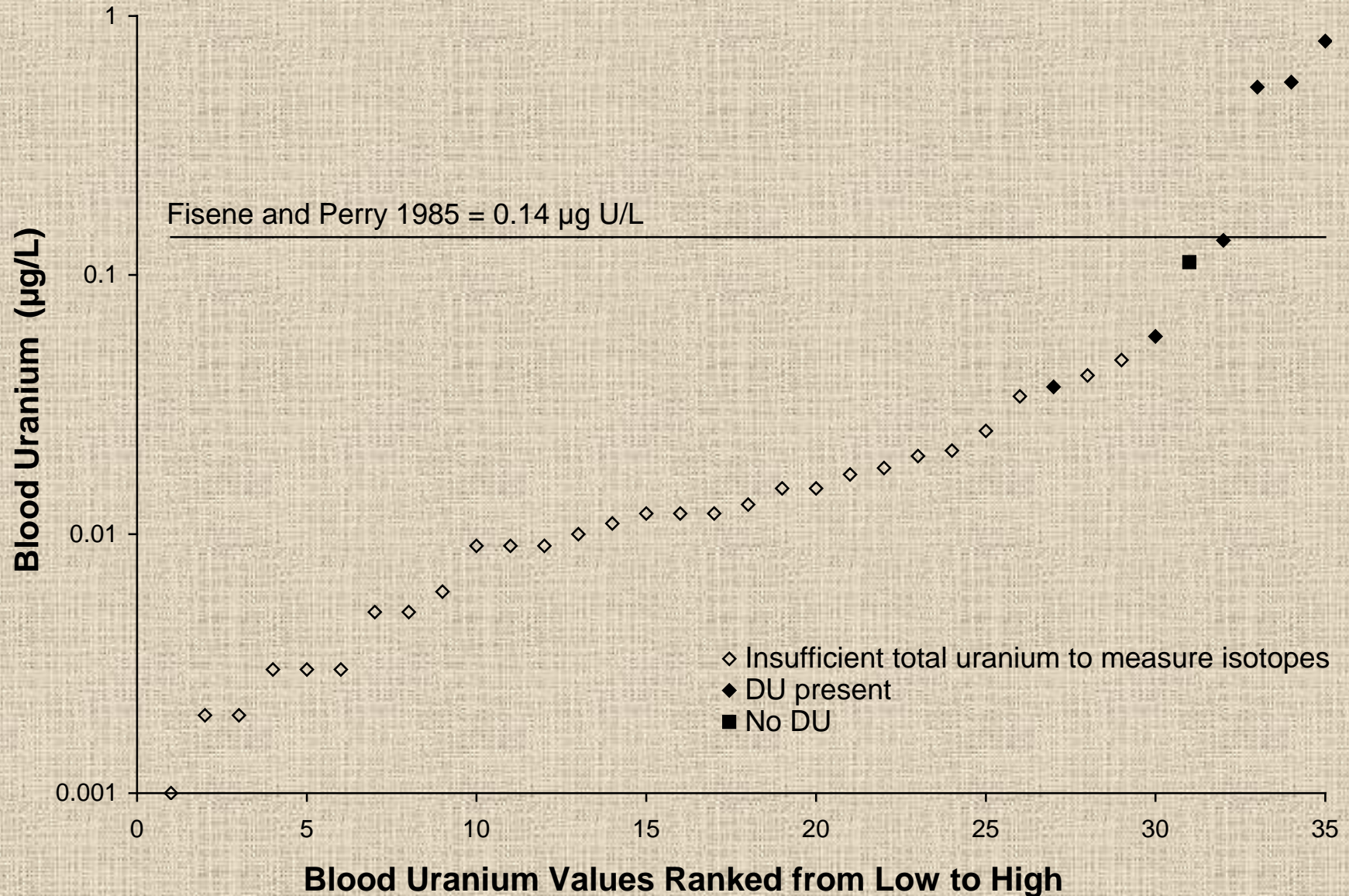


Correlation between Urine and Blood Uranium

When Urine U > 0.1 $\mu\text{g/g}$ Creatinine



Blood Uranium Values from the 2007 Cohort



Fisene and Perry (1985) Mean U concentration in blood of residents of NYC with no known occupational exposure to U

Radiation Dose Estimate from Whole Body Counting

- Nine veterans with whole body measurements above background
- Radiation dose estimates calculated using ICRP 30 Biokinetic model for U
 - 0.01 to 0.11 rem/year
 - 0.61 to 5.33 rem/50 years
- Public dose limit: 0.1 rem/year
- Occupational limit: 5 rem/year

Health Surveillance Results from 2009 Visit

Demographic Characteristics of the 2009 Participants Compared to All Participants

	2009 Cohort (n = 35)		All GWI Participants (n = 79)	
	N	%*	N	%
RACE				
African American	12	34%	24	30%
Asian American	1	3%	1	1%
Caucasian	20	57%	45	57%
Hispanic	2	6%	8	8%
Native American			1	1%
AGE**	43.62 ± 5.35		43.12 ± 4.80	

* May not add to 100% due to rounding

** Mean age a time of 2009 evaluation (± standard deviation)

Health Surveillance Protocol

- Complete history (medical, social, family, reproductive, occupational exposure, partner)
- Extensive laboratory studies (hematology, serum chemistry, neuroendocrine, urinalysis, urine, semen and blood uranium, renal markers, semen analysis, bone metabolism)
- Chromosomal analysis (HPRT, PIG-A, FISH, micronulcei)
- Neurocognitive testing
- Dermatologic testing for hypersensitivity to U
- Focus group/risk communication

Summary of Renal Effect Measures

Proximal Tubule Markers – 2009 Cohort

2009 Laboratory test (normal range)	Low Mean Uranium Group ^a (mean ± SE)	High Mean Uranium Group ^b (mean ± SE)	Mann- Whitney <i>p</i>
Urine β_2 microglobulin (0-0.3 mg/L)	0.10 ± 0.02	0.10 ± 0.01	0.50
Urine intestinal alkaline phosphatase (IAP) (<2 U/g creatinine)	0.20 ± 0.04	0.22 ± 0.04	0.79
Urine <i>N</i> -acetyl - β -glucosaminidase (NAG) (<5 U/g creatinine)	0.68 ± 0.23	0.45 ± 0.05	0.74
Urine total protein (1-150 mg/24 h)	110.24 ± 18.15	127.43 ± 16.80	0.15
Urine micro-albumin (<25 mg/g cre) ^c	3.36 ± 1.24	4.39 ± 2.48	0.39
Urine retinol binding protein (<610 μ g/g cre)	33.23 ± 4.32	35.51 ± 8.37	0.79

^a < 0.10 μ g/g creatinine (n=21)

^b \geq 0.10 μ g/g creatinine (n=14)

^c Low n = 18, High n = 12

Summary of Renal Parameters 1994-2009

Renal parameter	Evaluation Year						
	1994	1997	1999	2001	2003	2005	2007
Urine creatinine	ns	ns	l>h ¹ (p=.07)	ns	ns	ns	ns
Urine calcium				ns	ns	ns	ns
Urine PO ₄				ns	ns	l>h (p=.10)	ns
Urine β -2 microglobulin	ns	ns	ns	ns	ns	ns	h>l (p=0.11)
Urine intestinal alkaline phosphatase (IAP)			ns	ns	ns	ns	ns
Urine N-acetyl- β -glucosa-minidase (NAG)			ns	ns	ns	ns	ns
Urine total protein		ns	ns	H>L	l>h (p=.21)	ns	ns
Urine microalbumin					ns	ns	ns
Retinol binding protein (RBP)		ns	ns	h>l (p=.06)	h>l ns ²	ns	h>l (p=.07)
Serum creatinine	ns	ns	ns	L>H	ns	ns	L>H
Serum calcium				ns	ns	ns	ns
Serum PO ₄				ns	H>L	l>h ns	-
Serum uric acid	ns	ns	ns	ns	ns	ns	-

L = Low urine uranium group (U < 0.1 μ g/g creatinine)

H = High urine uranium group (U > 0.1 μ g/g creatinine)

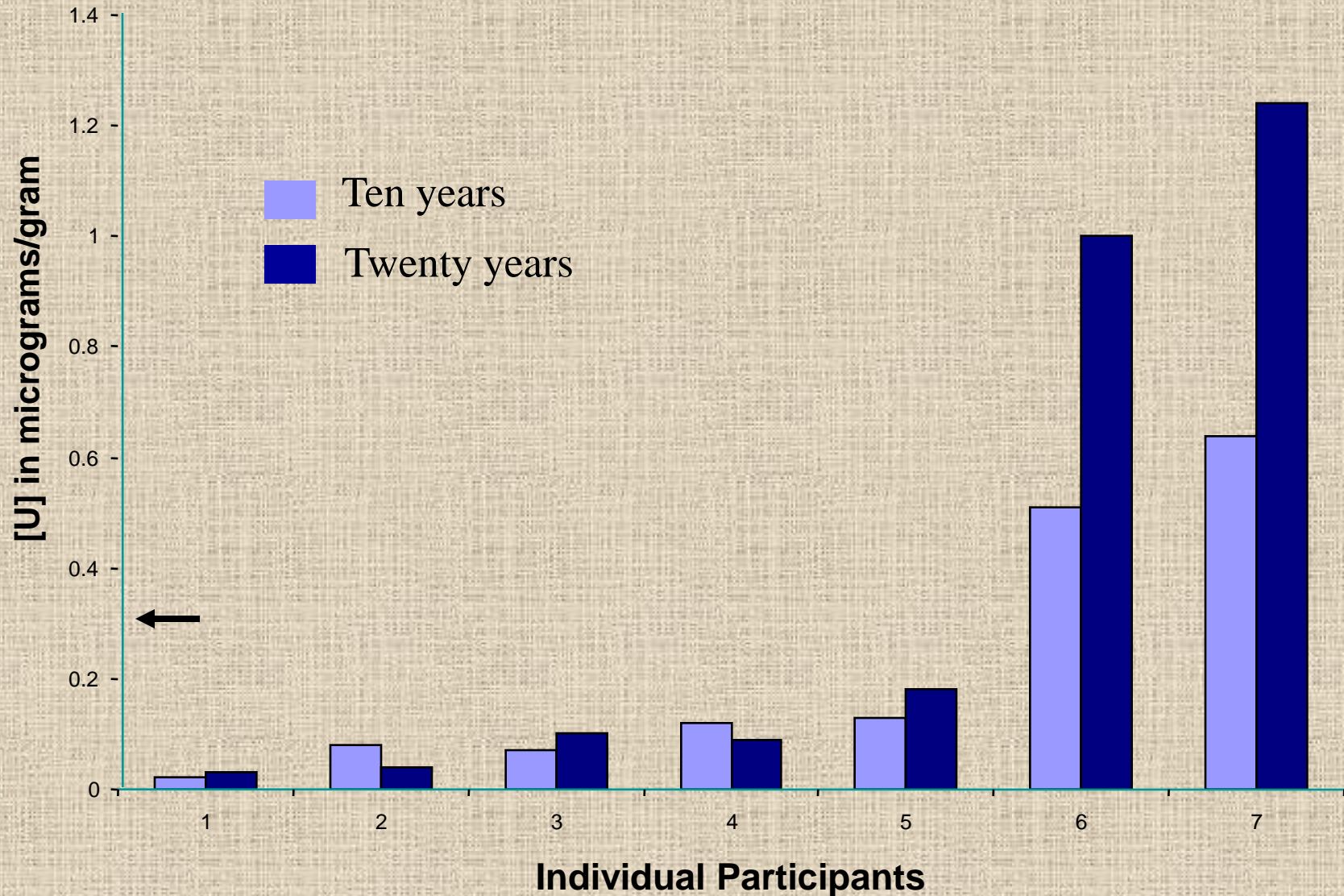
ns = no significant differences between groups

¹ Lower case letters = non-significant findings

² High uranium group 80.5 μ g/g creatinine \pm 51.4, low uranium group 27.3 μ g/g creatinine \pm 3.1, p=.54



Predicted Kidney Uranium Concentrations



Summary of Genotoxicological Measures

Summary of Differences in Genotoxicity Parameters across Evaluations

Genotoxicity Parameter	Evaluation Year							
	1994	1997	1999	2001	2003	2005	2007	2009
Sister chromatid exchange (SCE)		l>h* ns	H>L**	l>h ns	ns	-	-	-
Chromosomal aberrations (CA)		ns	ns	H>L	ns	ns	ns	-
Hypoxanthine-guanine phosphoribosyl transferase (HPRT)				h>l ns	h>l ns	h>l ns	ns	ns
Mutation frequency								
Mutation frequency adjusted for cloning efficiency					ns	ns	ns	ns
Mutation frequency adjusted for cloning efficiency and age					ns	ns	ns	ns
Fluorescent in-situ hybridization (FISH); Mean number of total mutations per subject in chromosomes 5, 7, 11, and 13						h>l p=.08	ns	ns
PIG-A								l>h p=.08
Micronuclei								ns

Low urine uranium group (U < 0.1 µg/g creatinine)

High urine uranium group (U ≥ 0.1 µg/g creatinine)

ns = no significant differences between groups

* lower case letters = non-significant findings

** upper case letters = significant findings (p ≤ 0.05)

Other Clinical Findings

- No clinically significant differences detected between low and high uranium exposure groups for
 - Semen characteristics
 - Neuroendocrine measures
 - Neurocognitive measures

Summary

- Subtle health effects observed in DU exposed veterans are most likely the result of chemical effects of U
 - Decreased reabsorption of filtered proteins in renal proximal tubules
 - Subtle changes in bone metabolism
- Weak genotoxicity results are consistent with epi studies examining carcinogenicity in U millers and miners
 - Mechanisms of DU genotoxicity may be a mix of chemical and radiologic effects
 - Potential for foreign body reaction in vicinity of embedded fragments is a concern

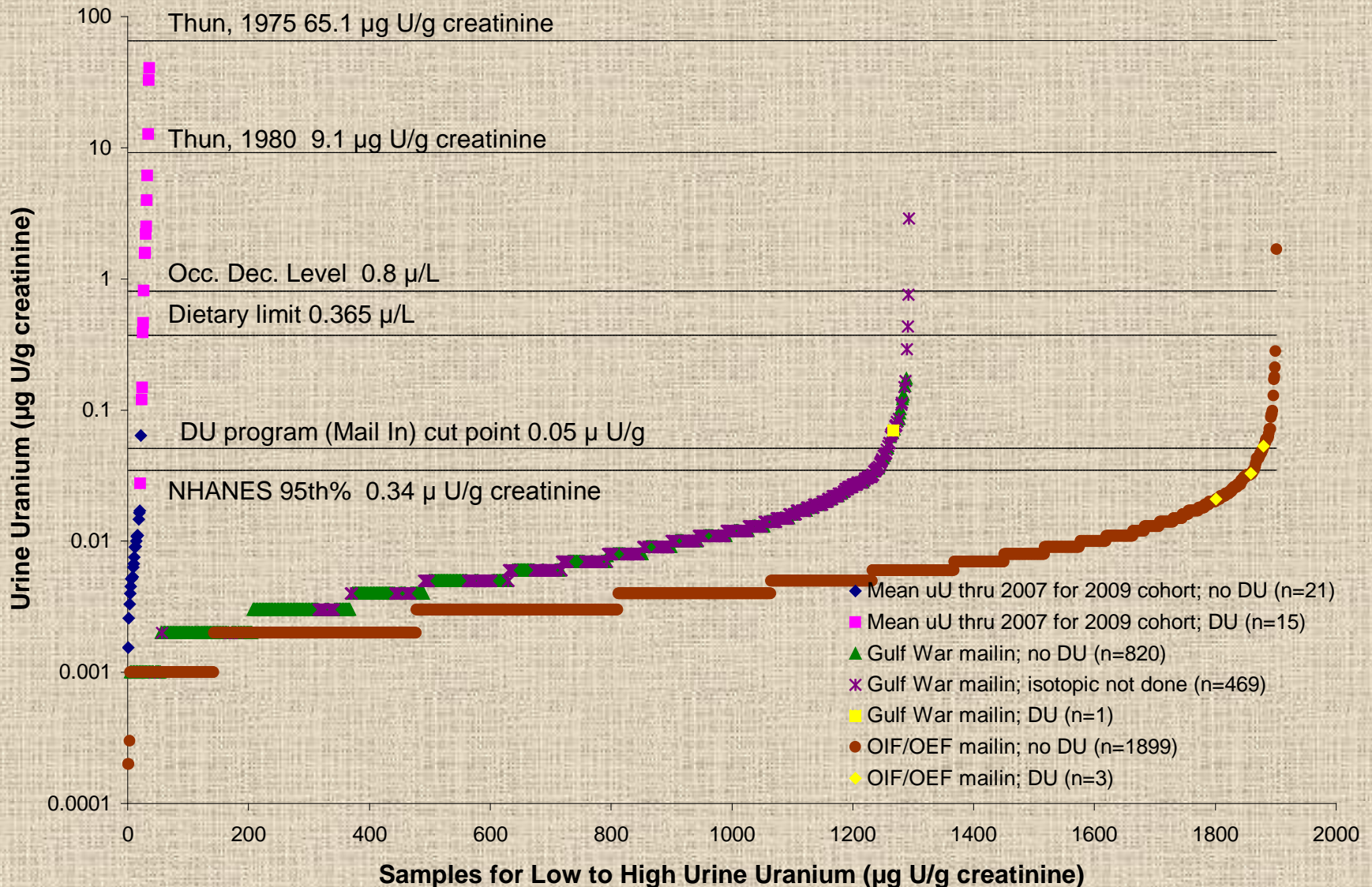
2nd Mission of the DU Follow-Up Program

- Since 1998:
To provide biologic monitoring by mail for uranium for all GWI and OIF veterans

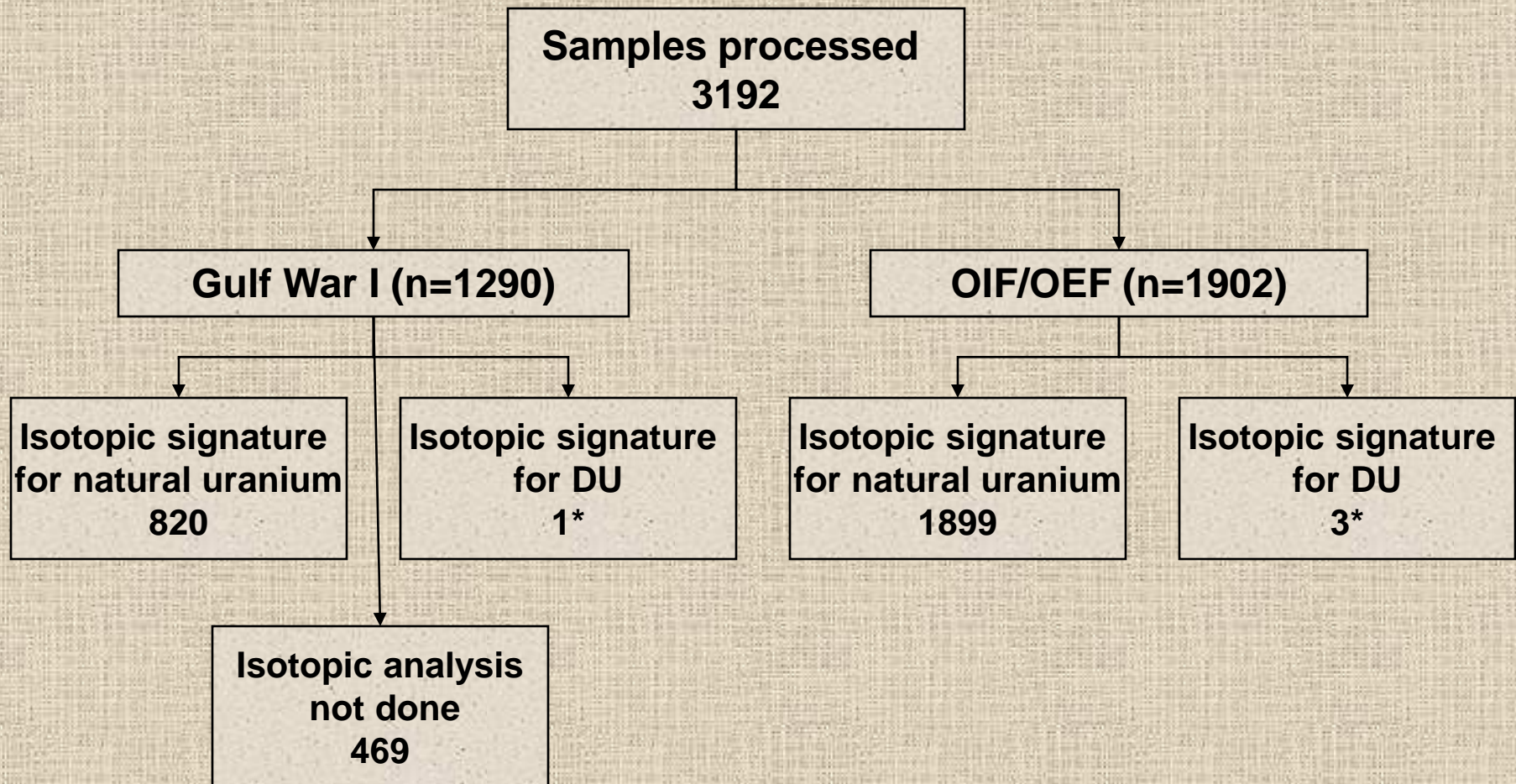
Purpose of the Urine Biomonitoring Program

- Determine urine uranium concentration in veterans from GWI and forward
- Passively survey for exposure scenarios linked to DU exposure other than friendly fire
- Provide assistance to veterans' primary care providers in interpreting results and answering veterans questions

Comparison of Urine Uranium Values from DUP, GWI and OIF(as of 10/31/10)



Results of OIF Urine Surveillance (as of 31 October 2010)

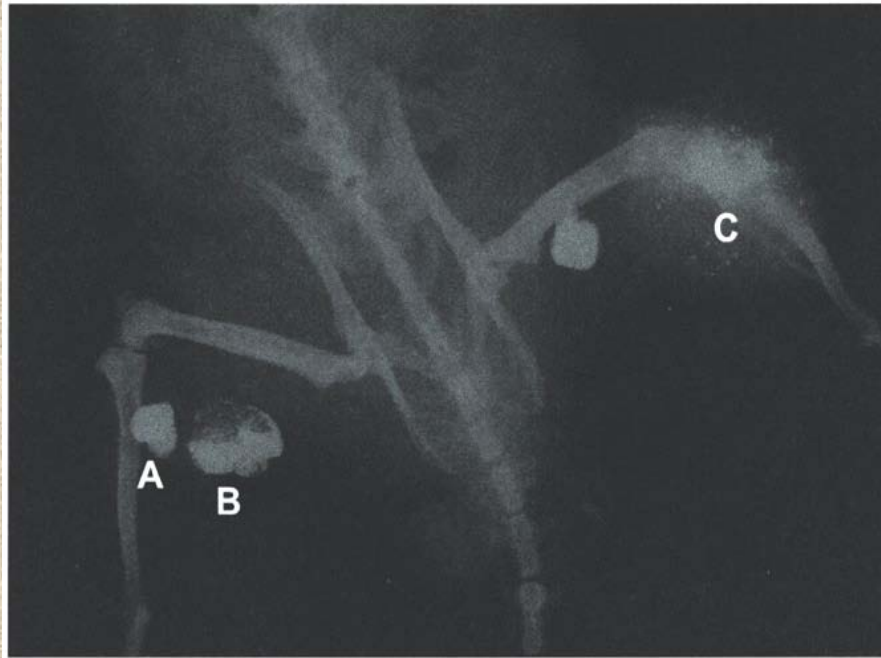


***All with DU signature were invited to enter the DU Follow-up Program.
Two from OIF/OEF declined but may be interested in future follow-up.**

Outstanding Questions

- Will health effects of DU develop in the cohort as it grows older?
- What are the health effects of concern related to effects of DU embedded fragments on adjacent tissues?
- Should even small pieces of DU shrapnel be removed?

Fate of DU Metal Fragments in Rat Muscle *in Situ*



Correlation of radiographic appearance with histologic appearance. (A) Thick fibrotic capsule with shards of corroded DU in lumen; (B) thick cellular capsule lined by squamous metaplasia, particles, and shards of corroded DU in wall and lumen; (C) particles and shards of disintegrated DU fragment scattered throughout a soft tissue sarcoma (Hahn et al, 2002).

1995 film



2001 film



Development of *in Situ* Surveillance Protocol

- Objective: To identify and manage (prevent) health effects related to fragment retention
 - Risk of the development of tumors at fragment sites
 - Foreign body effects?
 - Medical implants (hip, knee joints; dental implants, etc)
 - Bullets
 - Chemical effects?

***In Situ* Imaging Methods for Surveillance of Fragments and Surrounding Tissue**

- Currently using x-ray films to look for changes in the shape and other physical characteristics of the fragments
- Exploring other available imaging methods for identifying pre-neoplastic lesions or primary stage tumors
 - Ultrasound
 - MRI
 - PET/CT